A Fast and Accurate Diagnostic Test for Severe Sepsis Using Kernel Classifiers

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Abstract: Severe sepsis occurs frequently in the intensive care unit (ICU) and is a leading cause of admission, mortality, and cost. Treatment guidelines recommend early intervention, however gold standard blood culture test results may return in up to 48 hours. Insulin sensitivity (SI) is known to decrease with worsening condition and inflammatory response, and could thus be used to aid clinical treatment decisions. Some glycemic control protocols are able to accurately identify SI in real-time.

A biomarker for severe sepsis was developed from retrospective SI and concurrent temperature, heart rate, respiratory rate, blood pressure, and SIRS score from 36 adult patients with sepsis. Patients were identified as having sepsis based on a clinically validated sepsis score (ss) of 2 or higher (ss = 0–4 for increasing severity). Kernel density estimates were used for the development of joint probability density profiles for ss $\geq$ 2 and ss < 2 data hours (213 and 5858 respectively of 6071 total hours) and for classification. From the receiver operator characteristic (ROC) curve, the optimal probability cutoff values for classification were determined for in-sample and out-of-sample estimates.

A biomarker including concurrent insulin sensitivity and clinical data for the diagnosis of severe sepsis (ss $\geq$ 2) achieves 69–94% sensitivity, 75–94% specificity, 0.78–0.99 AUC, 3–17 LHR+, 0.06–0.4 LHR-, 9–38% PPV, 99–100% NPV, and a diagnostic odds ratio of 7–260 for optimal probability cutoff values of 0.32 and 0.27 for in-sample and out-of-sample data, respectively. The overall result lies between these minimum and maximum error bounds. Thus, the clinical biomarker shows good to high accuracy and may provide useful information as a real-time diagnostic test for severe sepsis.

Keywords: sepsis, insulin sensitivity, model-based control, non-parametric, classification, characteristic curves, discrimination, likelihood, accuracy, decision support systems

1. INTRODUCTION

Severe sepsis is a serious medical condition characterized by systemic inflammatory response syndrome (SIRS) and organ failure due to infection (Bone et al. 1992). In the adult intensive care unit (ICU), severe sepsis has an 11–15% incidence, 30–60% mortality rate, $22,100 USD average cost per case, $16.7 billion USD annual total cost, and 1.5% projected annual increase (Angus et al. 2001). Current sepsis management guidelines recommend treatment within 6 hours of confirmed infection (Levy et al. 2003). However, gold standard blood culture diagnostic test results return in 24–48 hours, by which time a serious complication may develop.

Early treatment has been reported to reduce mortality from 46.5% to 30.5% (Rivers et al. 2001). Alternative diagnostic tests based on identifying potential molecular markers for sepsis have not yet demonstrated sufficient performance to be routinely used in clinical practice (Pierrakos & Vincent 2010). Thus, there remains a serious need for fast and accurate severe sepsis diagnostic tests.

Model-based insulin sensitivity (SI) has been observed to indicate the severity of illness, decrease with worsening condition (Chambrier et al. 2000), and increase with improvement (Chase et al. 2008; Langouche et al. 2007). A clinically validated glucose-insulin physiological model that is able to identify hourly SI has been used to develop blood glucose control management protocol for critically ill patients (Chase et al. 2007).

Previous work has shown model-based hourly SI as a potential biomarker for septic shock (Blakemore et al. 2008). A biomarker including hourly SI and available bedside clinical data has differentiated severe sepsis in a cohort of adult ICU patients (Lin et al. 2010). Thus, model-based SI in combination with clinical measurements offers unique potential for early, rapid detection of severe sepsis or sepsis shock in clinical "real-time".

This outcome can be achieved by creating a classification method to identify an unknown patient hour as severe sepsis or non-severe sepsis. Thus, a method utilising kernel density estimates to develop joint density profiles for severe sepsis and non-severe sepsis and for classification is presented. Standard diagnostic test performance outcomes (Fischer et al. 2003) are reported to evaluate the SI and clinical biomarker joint density diagnostic test performance, as compared to the clinically validated patient sepsis score.

2. METHODS

Retrospective clinical data including hourly insulin sensitivity, temperature, heart rate, respiratory rate, blood pressure, and SIRS score were collected from adult sepsis patients. Kernel density estimates were used for the development of joint probability density profiles for severe sepsis and non-severe sepsis hours and for classification. Diagnostic test properties were analyzed by comparing test outcomes to a clinically validated sepsis score (ss).

2.1 Sepsis score (ss) and cohort

Severe sepsis is a systemic inflammatory response syndrome (SIRS) and organ failure due to infection (Bone et al. 1992). Patient sepsis score is defined by ACCP/SCCM guideline definitions (Levy et al. 2003). The defined criteria include SIRS and the Sepsis-related Organ Failure Assessment (SOFA) score (Vincent et al. 1996) found in Appendix A.

Clinical data was obtained from n = 36 sepsis patients admitted to the medical ICU in Christchurch Hospital. Each patient was on the SPRINT blood glucose control protocol (Chase et al. 2008), providing 9286 total patient hours of model-based hourly SI. Additional clinical data collected includes: temperature, heart rate, respiratory rate, blood pressures, and SIRS score. Patient hours were removed if any of these concurrent clinical data were not reported on the medical record. Data hours that are unambiguously without infection (i.e., ss = 0 and SIRS < 2) were removed, providing a new total of 6071 hours of data useful for developing and testing the classifier. Notably, each sepsis patient had episodes both with sepsis (ss ≥ 1) and non-sepsis (ss = 0). Thus, each patient provides periods of control to changes in their physiological condition and sepsis score (ss = 0–4).

Cohorts are defined as severe sepsis (ss ≥ 2) and non-severe sepsis (ss < 2). Notably, this study includes particular patient hours which are normally omitted in other studies, as they cannot be classified unambiguously (Kuster et al. 1998). Such omissions would have resulted in a case-control design. Case-control design has been identified as the most important source of bias for overestimating test accuracy (Lijmer et al. 1999). Importantly, no such omissions are made in this study.

The clinical reality of early sepsis management in the ICU deviates from the use of blood culture alone as an absolute gold standard. Rather, the gold standards clinicians use are confirmed infection with clinical evidence and unconfirmed infection without clinical evidence. Most clinicians are able to distinguish between a severely ill patient and a healthy control. However, clinicians seek help for exactly the ambiguous cases. Thus, this set of data provides hour to hour evaluation of the SIRS/SS/SOFA score, as an effective objective gold standard to test the diagnostic ability of the developed classification system.

Figures 1–5 provide raw data in a discrete form consistent with original patient medical records and normalized to the cohort size. Each data set has a sum of 1. When applicable, relevant SIRS and SOFA classification criteria definitions are shown.

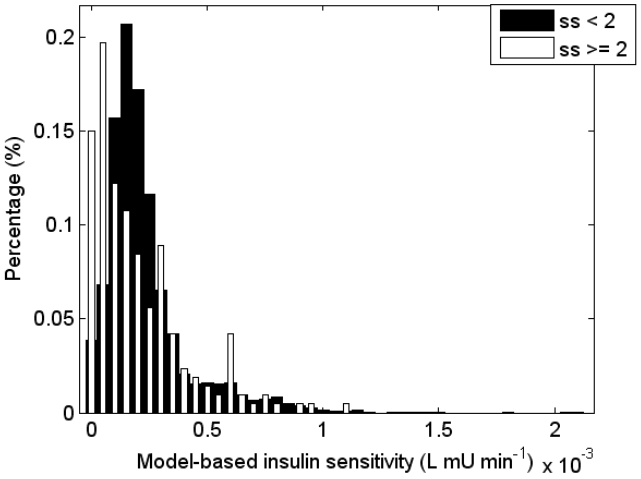

Fig. 1. Model-based insulin sensitivity (SI) raw data, grouped by severe sepsis and non-severe sepsis cohorts.

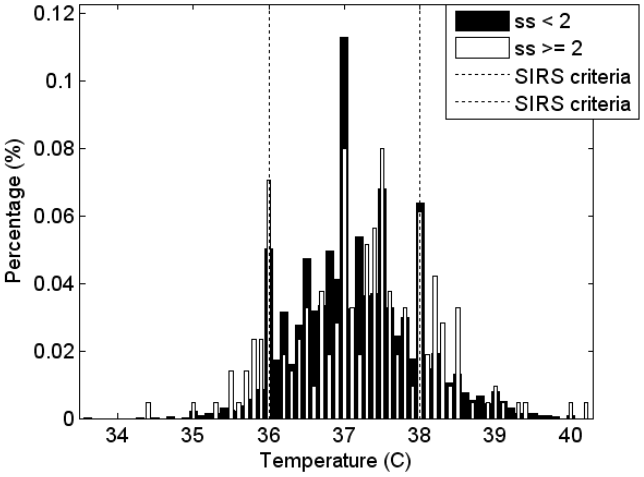

Fig. 2. Temperature raw data. One of the SIRS criteria is temperature < 36° C or > 38° C.

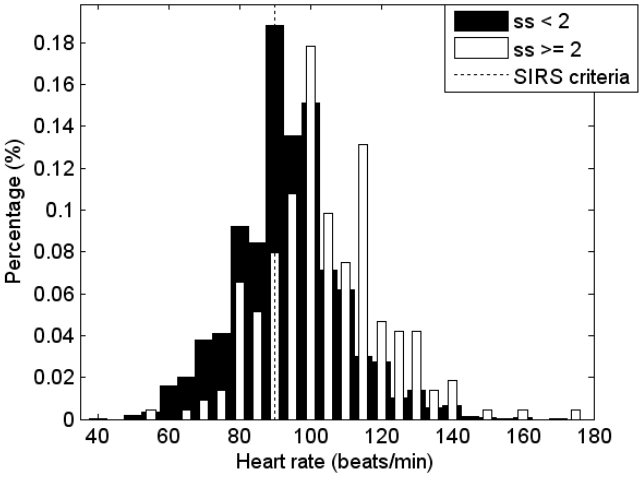

Fig. 3. Heart rate raw data. One of the SIRS criteria is heart rate > 90 beats/min.

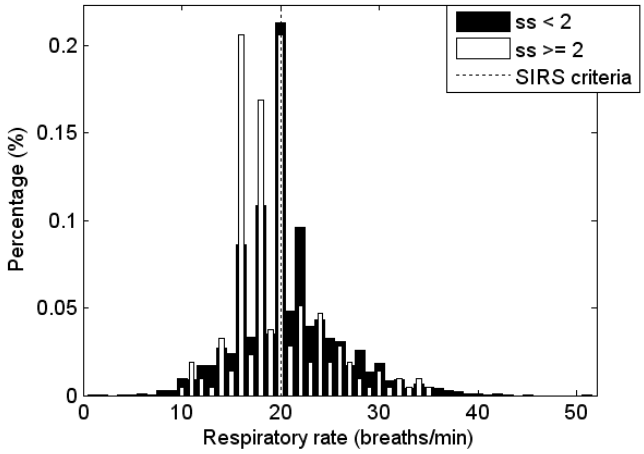

Fig. 4. Respiratory rate raw data. One of the SIRS criteria is respiratory rate > 20 breaths/min or mechanically ventilated.

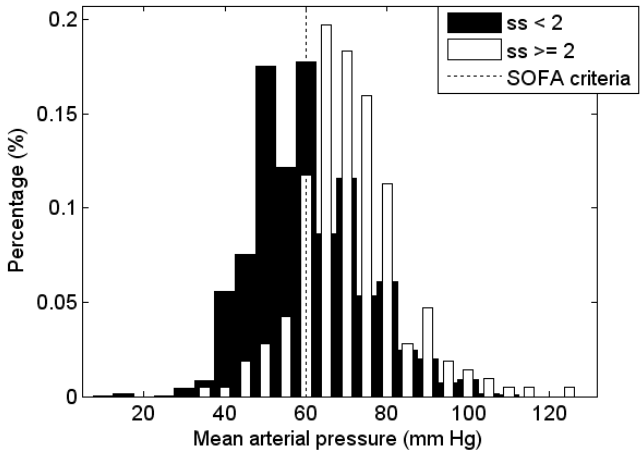

Fig. 5. Mean arterial pressure (MAP) raw data. One of the SOFA criteria is MAP < 60 mm Hg.

It can be observed that between severe sepsis and non-severe sepsis cohorts, SI and respiratory rate decrease with increased ss, while heart rate and mean arterial pressure increase, and temperature remains undistinguished between cohorts. Thus, some clinical data may contribute more strongly to discriminating patient sepsis states.

2.2 Classification

Kernel density estimates can be used for classification and identification of potential diagnostic biomarkers (Moorhead et al. 2008). Clinically validated sepsis scores at each patient hour are used to develop probability density profiles for each of the two data sets: Groups *j* and *k*, for each clinical predictor. In this diagnostic analysis, *j* and *k* would be the severe sepsis (ss ≥ 2) and non-severe sepsis (ss < 2) data. A patient hour is then tested against the established datasets, with the result being a classification into either Group *j* or *k*.

For each given patient hour, the joint probability density for Groups *j* and *k* of each clinical predictor are compared. Log transforms were used to remove natural data bounds from model-based SI, respiratory rate, diastolic blood pressure, and SIRS.

Let x_0 denote the value of a single clinical predictor at the given hour, and $\hat{f}_j(x_0^*)$ and $\hat{f}_k(x_0^*)$ denote the joint probability densities of Group *j* and *k*, respectively, at the clinical predictor values at that hour. Thus, for a given hour of clinical data, the joint probability density of these data being from a severe sepsis or non-severe sepsis cohort is compared for classification.

For each hour, the probability of the given data value being from Group *j*, given the data value obtained at that hour is x_0 is defined

$$\hat{P}r(j|x_0^*) = \frac{\hat{\pi}_j \hat{f}_j(x_0^*)}{\hat{\pi}_k \hat{f}_k(x_0^*) + \hat{\pi}_j \hat{f}_j(x_0^*)} \quad (1)$$

where $\hat{\pi}$ is the prior probability of the sample being in that group. In this case, the prior probabilities are set to 0.5, as no reliable historical information of the prior probability for these cohorts is known. Thus, the prior probability does not impact classification. If the ratio in (1) is greater than a specified probability threshold, then the sample is classified as being in the numerator (Group *j*), otherwise it is classified as being in Group *k*.

As well as classification, an estimate of prediction error is required. In-sample estimates and out-of-sample estimates using the stratified bootstrap method (take out 20% to test against) and 1000 bootstraps were used to estimate the classification model prediction minimum and maximum error bounds, respectively.

2.3 Sensitivity and specificity

Standard diagnostic test properties are reported as recommended by Fischer et al. (2003). An optimal probability cutoff value was obtained from the receiver operator characteristic (ROC) curve, which best discriminates severe sepsis (ss ≥ 2) and non-severe sepsis (ss < 2) cohorts. A contingency matrix is used to provide sensitivity and specificity with respect to a clinically validated sepsis score.

2.4 Predictive values and likelihood ratios

Likelihood ratios and predictive values provide the probability that a patient with a given test result is actually infected (Jaeschke et al. 1994a; Jaeschke et al. 1994b). Predictive values represent the proportion of test results which correctly identify severe sepsis, positive predictive value (PPV), and non-severe sepsis, negative predictive value (NPV). Note that the major determinant of the predictive value is the infection prevalence (Smith et al. 2000).

An alternative method to assess the predictive properties of a test is the likelihood ratio (Jaeschke et al. 1994a). Likelihood ratios are independent from prevalence. The likelihood ratio is the ratio of the probability that a specific test result is obtained in patients with severe sepsis divided by the probability of obtaining the same test result in non-severe sepsis patients (Fischer et al. 2003).

The likelihood ratio for a positive test result (LHR+) could be calculated as

$$LHR+ = \frac{sensitivity}{(1-specificity)}. \quad (2)$$

The likelihood ratio for a negative test result (LHR-) is obtained as

$$LHR- = \frac{(1-sensitivity)}{specificity}. \quad (3)$$

Multilevel likelihood ratios (MLR) are also presented to allow which levels of test results yield clinically important information, and which levels of test results do not (Jaeschke et al. 1994b).

2.5 The receiver operator characteristic curve and the diagnostic odds ratio

A single measure that summarizes the discriminative ability of a test across the full range of probability cutoff values, and is also independent of prevalence, is the area under the ROC (AUC). Reporting AUCs allows valuable statistical comparison of diagnostic tests (Hanley & McNeil 1983). It is particularly useful if applied to the same patient population for the same diagnostic question.

Finally, an alternative way to compare tests that is also relatively independent of prevalence is by means of the diagnostic odds ratio (Lijmer et al. 1999). The diagnostic odds ratio (DOR) is calculated as

$$DOR = \frac{LHR+}{LHR-}. \quad (4)$$

3. RESULTS AND DISCUSSION

3.1 Sepsis score (ss) and cohort

The prevalence of severe sepsis (ss ≥ 2) is 3.5% (213 hours of the 6071 total hours) in the data collected for this study. Such a low prevalence is clinically realistic throughout sepsis patient hourly data. Table 4 shows the prevalence for each ss value.

Table 4. Sepsis score (ss) prevalence for original and filtered (removed ss = 0 when SIRS < 2) data

ss	0	1	2	3	4
original	4186 (45.1%)	4861 (52.4%)	91 (1.0%)	88 (1.0%)	60 (0.7%)
filtered	1558 (25.7%)	4300 (70.8%)	85 (1.4%)	79 (1.3%)	49 (0.8%)

3.2 Sensitivity and specificity

The optimal probability cutoff values for the kernel classifier are 0.32 and 0.27 for in-sample and out-of-sample estimates, respectively. The optimal cutoff value has important bearing on the following measures of test accuracy. The ROC curves are shown in Figure 6. The contingency matrices are shown on Tables 5 and 6.

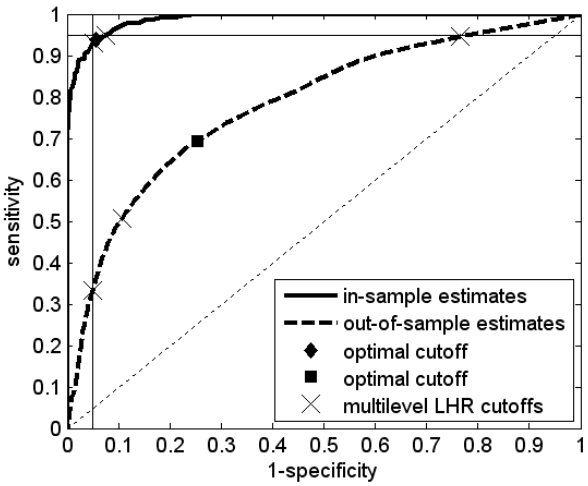

Fig. 6. ROC curves for the joint density kernel classifier, with optimal probability cutoff values shown. The overall performance lies between these maximum error bounds.

Table 5. Contingency matrix for in-sample estimates (total 6071 hours)

cutoff 0.32	ss ≥ 2 213 hours	ss < 2 5858 hours	prevalence 3.5%
test positive 527 hours	TP = 200 (3.3%)	FP = 327 (5.4%)	PPV 38%
test negative 5544 hours	FN = 13 (0.2%)	TN = 5531 (91.1%)	NPV 100%
	sensitivity 94%	specificity 94%	AUC 0.99
log odds ratios	LHR+ 17	LHR- 0.06	DOR 260

Table 6. Contingency matrix for out-of-sample estimates (1000 bootstraps, total 1,215,000 hours)

cutoff 0.27	ss ≥ 2 43,000 hours	ss < 2 1,172,000 hours	prevalence 3.5%
test positive 326,337 hours	TP = 29,817 (2.5%)	FP = 296,520 (24.4%)	PPV 9%
test negative 888,663 hours	FN = 13,183 (1.1%)	TN = 875,480 (72.1%)	NPV 99%
	sensitivity 69%	specificity 75%	AUC 0.78
log odds ratios	LHR+ 3	LHR- 0.4	DOR 7

The test performs with 69%–94% sensitivity and 75–94% specificity. The overall result lies between these maximum estimate bounds. The kernel classifier correctly identifies the majority of ss ≥ 2 and ss < 2 patient hours.

3.3 Predictive values and likelihood ratios

The test has 9–38% PPV and 99–100% NPV. The majority of negative outcomes are from true negative (TN) patient hours. PPV is low due to the low disease prevalence (3.5%). However, the low ratio of ss ≥ 2 to ss < 2 is clinically realistic for hour to hour data during patient length of stay.

The major determinant of predictive values is the prevalence of infection (Smith et al. 2000). Thus, predictive values depend not only on the test's properties, but also on the prevalence of disease in the population. Therefore they do not represent the test's inherent accuracy by themselves.

The test performs with 3–17 LHR+ and 0.06–0.4 LHR-. This can be interpreted to mean that the probability of obtaining an in-sample probability greater than 0.32 is obtained approximately 17 times more often from a patient with ss ≥ 2 than from a patient with ss < 2. A likelihood value of 1 implies the test result is equally likely to occur among patients with the disease as in patients without the disease.

Tests with LHR+ > 10 or LHR- < 0.1 have the potential to alter clinical decisions (Jaeschke et al. 1994b). Tests with 5–10 LHR+ or 0.1– 0.2 LHR- often provide useful information. Tests with LHRs ranging from 0.33–3 rarely alter clinical decisions. Thus, this test may have the potential to alter clinical decisions for the positive identification of severe sepsis. This test may also provide useful additional information for determining non-severe sepsis.

MLR results across the range of probability cutoff values within sensitivity or specificity > 95% are shown in Table 7. Note the ROC probability cutoff values start from 0 at the top right corner of Figure 6. The disadvantage of dichotomizing test results is that useful information may be lost, as a test result returned may be negative, indeterminate, or positive.

3.4 The receiver operator characteristic curve and the diagnostic odds ratio

The ROC curves have 0.78–0.99 AUC. Perfect tests yield an AUC of 1.0. A test with an AUC > 0.9 has high accuracy, while 0.7–0.9 indicates moderate accuracy, 0.5–0.7 low accuracy, and 0.5 a chance result (Swets 1988). Therefore, this test performs with good to high accuracy.

For tests with intermediate to good discriminative properties (0.75–0.85 AUC), the curve shape requires consideration. Accepting a margin of error of 5% (sensitivity or specificity > 95%), curve probability cutoff values in the ROC upper horizontal rectangle are useful to rule-in infection, while points on the curve in the ROC left, vertical rectangle assist in ruling-out infection in Figure 6.

Probability values from 0–0.29 and 0–0.02 rule in infection, while probability values from 0.33–1 and 0.71–1 rule out infection for in-sample and out-of-sample estimates, respectively. These values define the range of probability values shown in the MLR in Table 7.

The test yields 7–260 DOR for the optimal probability cutoff values. Potentially useful tests have DOR > 20 (Fischer et al. 2003). Thus, this test may be potentially useful.

Table 7. Multilevel likelihood ratios (MLR)

	cutoff value	LHR+	LHR-	DOR
in-sample	0.29	13	0.06	226
	0.32	17	0.06	260
	0.33	18	0.07	244
out-of-sample	0.02	1	0.2	5
	0.27	3	0.4	7
	0.5	5	0.6	9
	0.71	7	0.7	10

4. CONCLUSIONS

Joint kernel density estimates for insulin sensitivity and concurrent clinical data, including temperature, heart rate, respiratory rate, blood pressure, and SIRS score provide a good to highly accurate diagnostic test for severe sepsis (ss ≥ 2). Some clinical data may contribute more strongly to patient diagnosis. At an optimal probability cutoff value for in-sample and out-of-sample estimates, the diagnostic test correctly classifies the majority of ss ≥ 2 and ss < 2 hours. Low PPV and high NPV are due to the low prevalence (3.5%) of ss ≥ 2 in the hourly data from a cohort where case-control design has been avoided. LHR and the AUC demonstrate that this test provides potentially useful information and may have the potential to alter clinical decisions towards severe sepsis diagnosis.

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Appendix A. SEPSIS SCORE CRITERIA

Table 1. SIRS criteria

score	criteria	
+ 1	temperature	< 36º C > 38º C
+ 1	heart rate	> 90 beats/min
+ 1	respiratory rate or $PaCO_2$	> 20 breaths/min < 32 mm Hg
+ 1	white blood cell count	< 4 x 10^9/L or > 12 x 10^9/L or > 10% immature granulocytes

Table 2. SOFA criteria

score	system	criteria	
+ 1	cardiovascular	MAP[a] or need for inotropes	< 60 mm Hg
+ 1	respiratory	PaO_2/FiO_2	<250 mm Hg/mm Hg <200 mm Hg/mm Hg with pneumonia
+ 1	renal	urine output	< 0.5 ml/kg/h
+ 1	blood	platelets	< 80 x 10^9/L or 50% drop in 3 days
[a]Mean arterial pressure			

Table 3. Sepsis score (ss) criteria

sepsis score		SIRS > 2	infection during stay	organ failure > 1	fluid resuscitation	inotrope present	inotrope dose > 0.2 mg min^{-1} kg^{-1}
0	normal						
1	sepsis	X	X				
2	severe sepsis	X	X	X	X		
3	septic shock	X	X	X	X	X	
4	refractory septic shock	X	X	X	X	X	X